Dimensions of pain catastrophizing and specific structural and functional alterations in patients with chronic pain: evidence in medication-overuse headache

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Abstract: We examined the neuroanatomical substrate of different pain catastrophizing (PC) dimensions (i.e. rumination; magnification; helplessness) in patients with medication-overuse headache (MOH). We included 18 MOH patients who were administered the Pain Catastrophizing Scale (PCS) and scanned in a 3T-MRI. We conducted whole-brain volumetric and resting-state functional connectivity (FC) analysis to examine the association between gray matter (GM) density and FC strength and PCS dimensions controlling for depression and anxiety. Higher total PCS score was associated with decreased GM density in precentral and inferior temporal gyrus, FC between middle temporal gyrus and cerebellum and FC between precuneus and inferior temporal gyrus, as well as between frontal pole and temporal fusiform cortex. Regarding PCS dimensions, we mainly observed the involvement of a) somatosensory cortex, supramarginal gyrus, basal ganglia, core default-mode network (DMN) in rumination; b) somatosensory , core DMN, dorsal medial prefrontal cortex (DMPFC)-DMN subsystem and cerebellum in magnification; and c) temporal regions, DMN and basal ganglia in helplessness. PC dimensions are associated with a specific structural and functional neuroanatomical pattern, which is different from the pattern observed when PC is considered as a single score. The involvement of basal ganglia and cerebellum needs further investigation.

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Dimensions of pain catastrophizing and specific structural and functional alterations in patients with chronic pain: evidence in medication-overuse headache

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Abstract

Objectives: We examined the neuroanatomical substrate of different pain catastrophizing (PC) dimensions (i.e. rumination; magnification; helplessness) in patients with medication-overuse headache (MOH).

Methods: We included 18 MOH patients who were administered the Pain Catastrophizing Scale (PCS) and scanned in a 3T-MRI. We conducted whole-brain volumetric and resting-state functional connectivity (FC) analysis to examine the association between gray matter (GM) density and FC strength and PCS dimensions controlling for depression and anxiety.

Results: Higher total PCS score was associated with decreased GM density in precentral and inferior temporal gyrus, **increased** FC between middle temporal gyrus and cerebellum and **reduced** FC between precuneus and inferior temporal gyrus, as well as between frontal pole and temporal fusiform cortex. Regarding PCS dimensions, we mainly observed the involvement of a) somatosensory cortex, supramarginal gyrus, basal ganglia, core default-mode network (DMN) in rumination; b) somatosensory **cortex**, core DMN, dorsal medial prefrontal cortex (DMPFC)-DMN subsystem and cerebellum in magnification; and c) temporal regions, DMN and basal ganglia in helplessness.

Conclusion: PC dimensions are associated with a specific structural and functional neuroanatomical pattern, which is different from the pattern observed when PC is considered as a single score. The involvement of basal ganglia and cerebellum needs further investigation.

Keywords: pain catastrophizing processes; voxel-based morphometry; functional connectivity; medication overuse; headache

INTRODUCTION

The perception of pain results from the coordinated activity in a number of brain regions (i.e. "pain matrix"), integrating sensory inputs with ongoing memories and internal representations (Apkarian, Bushnell et al. 2005, Garcia-Larrea and Peyron 2013). Pain catastrophizing (PC) is an expansion of a maladaptive cognitive **response** during actual or perceived painful stimulation (Beck 1979, Ellis 1994) and influences pain perception. PC comprises of negative cognitive and emotional processes of helplessness and rumination about pain-related symptoms and magnification of pain complaints (Sullivan, Thorn et al. 2001).

This set of negative processes negatively contributes to pain severity in several chronic pain syndromes (Edwards, Cahalan et al. 2011) and influences pain-related outcomes, since it is a risk factor for long-term and more severe pain, physical disability and depression (Vlaeyen and Linton 2000, Edwards, Cahalan et al. 2011, Khan, Ahmed et al. 2011) and the single most important pre-treatment risk factor for the ineffectiveness of pain-relieving therapies (Karels, Bierma-Zeinstra et al. 2007). PC and mood status are important factors in understanding the migraine pain (Goli, Asghari et al. 2016) whereas catastrophizing has been associated with impaired functioning and quality of life in migraineurs independent of migraine characteristics and other demographic and psychological variables (Holroyd, Drew et al. 2007). Although the most characteristic dimensions of PC (i.e. magnification, helplessness, rumination) are positively related to each other (Craner, Gilliam et al. 2016) (Sullivan, Bishop et al. 1995), pain intensity and pain outcome is differentially affected by these components (e.g. neuropathic pain (Sullivan, Lynch et al. 2005); mixed diagnoses of chronic pain (Craner, Gilliam et al. 2016)). However, the majority of studies relies on a total PC score, although they use measures (i.e. Pain Catastrophizing Scale (PCS) (Sullivan, Bishop et al. 1995)) that enable the extraction of separate dimensions.

The rise of several neuroimaging techniques offers the potential for breakthroughs in the understanding of pain perception and modulation in health and disease (Moayedi, Salomons et

al. 2018). However, few studies have examined the neuroimaging substrate of PC (fibromyalgia (Gracely, Geisser et al. 2004, Lee, Protsenko et al. 2018), migraine (Hubbard, Khan et al. 2014), medication-overuse headache (MOH) (Chanraud, Di Scala et al. 2014)) using functional (Gracely, Geisser et al. 2004) or multimodal (Chanraud, Di Scala et al. 2014, Hubbard, Khan et al. 2014, Lee, Protsenko et al. 2018) techniques and highlight the involvement of primary and secondary somatosensory areas, prefrontal regions, anterior cingulate cortex (ACC), insula, and subcortical structures (i.e. basal ganglia, thalamus, hippocampus), as well as default-mode network (DMN) nodes. Only one study so far in patients who underwent lumbar disk surgery examined specific dimensions of PC in association with GM changes (Chehadi, Suchan et al. 2017); apart from the relation of PC with GM density in areas involved in processing attentional, sensory and affective aspects of pain, the authors provide preliminary evidence for brain structures specifically related to magnification and helplessness.

Based on the above-mentioned points and the clinical relevance of identifying the brain circuitry related to PC as a first step to further design specific interventions, the aim of the present study is to investigate the structural and functional substrate of rumination, magnification and helplessness in patients with MOH. PC may worsen the experience of pain through physiological and neural pathways by enhancing it via differential patterns of brain activation (Rhudy, Martin et al. 2011) and by modulating the analgesic effects of medications affecting the endogenous opioid system (King, Goodin et al. 2013) (Sturgeon and Zautra 2013). Thus, the inclusion of patients with MOH as a clinical group to study neuroanatomical substrates of PC dimensions seems to be of outmost importance.

MATERIAL AND METHODS

Participants

This cross-sectional study was approved by the ethical committee of the hospital and all patients provided informed consent for their participation according to the Declaration of Helsinki. Eighteen patients with MOH who had migraine as the underlying primary headache were enrolled. Inclusion criteria were a) absence of neurological disorders (other than MOH); b) absence of severe psychiatric disorders (e.g. major depression, schizophrenia) based on patients' records and structured clinical interview by experienced psychiatrist; c) absence of severe or untreated heart or metabolic diseases; d) absence of known severe brain abnormalities or contra-indications for MRI scanning. Patients were recruited from the outpatient headache clinic at the First Department of Neurology, Aeginition Hospital. All patients fulfilled the IHS Classification ICHD-II (2013) criteria (Headache Classification Committee of the International Headache 2013) for MOH and migraine without aura. Two patients had a current comorbid bipolar disorder and obsessive-compulsive disorder. Headache days/month and medication/month were recorded based on headache diaries, migraine duration (years) was retrospectively evaluated in all patients. Medication overuse included simple analgesics, non-steroidal anti-inflammatory drugs, triptans, opioids and combination analgesics.

Psychometric assessment

Pain Catastrophizing: The 13-item PCS (Sullivan, Bishop et al. 1995), rated on a 0-4 Likert scale, was administered to all patients to assess the severity of PC. The PCS consists of three subscales that evaluate different dimensions, i.e. rumination (PCS-R), magnification (PCS-M) and helplessness (PCS-H). PCS-R includes items that describe ruminative thoughts, worry, and an inability to inhibit pain-related thoughts. PCS-M includes items that reflect magnification of the unpleasantness of pain situations and expectancies for negative outcomes. Finally, PCS-H includes items that reflect the inability to deal with painful

situations. A total PCS score (PCS-T) of 30 has been proposed as a clinically relevant level of catastrophizing (Sullivan 2009); thus, patients who scored ≥30 on the PCS-T were categorized as high catastrophizers.

Mood: The Hospital Anxiety and Depression Scale (HADS (Zigmond and Snaith 1983, Michopoulos, Douzenis et al. 2008)) was used to evaluate patients' depressive and anxiety symptoms during the past two weeks before the MRI scanning.

MRI data acquisition

All participants underwent the same imaging protocol on a 3T Achieva TX Philips manufactured MRI scanner (Philips, Best, the Netherlands) at Radiology and Medical Imaging Research Unit, Second Department of Radiology, Attikon Hospital. The protocol included a 3D high resolution T1 (3D-HR-T1) weighted sequence (repetition time (TR): 9.9 ms, time echo (TE): 3.7 ms, flip angle: 7^0, voxel size 1x1x1 mm, sagittal orientation), a T2* weighted gradient echo combined with echo planar imaging for resting state functional magnetic resonance imaging (rs-fMRI) with whole brain coverage (TR: 2500 ms, TE: 30 ms, flip angle: 90^o, acquisition voxel size 3x3x3 mm^3 and sensitivity encoding reduction factor of two), as well as T2 weighted fluid attenuated inversion recovery (T2-FLAIR) sequence. During the rs-fMRI scan, participants were instructed to lie still with their eyes closed. An experienced neuroradiologist considered major anatomical abnormalities on participants' T1-weighted and T2-FLAIR images of the whole brain. In addition, all data were checked slice by slice by an experienced MR physicist to identify motion or other type of artifacts.

MRI data analysis

Voxel-based morphometry (VBM) analysis

Volumetric analysis was performed using the computational anatomy toolbox (CAT12), a toolbox of statistical parametric mapping (SPM12; Wellcome Department of Cognitive Neurology, www.fil.ion.ucl.ac.uk/spm/software/spm12) implemented on MATLAB R2015b

(The MathWorks, Natick, USA). All 3D-HR T1 images were initially segmented into GM, white matter (WM) and cerebrospinal fluid, and then were normalized using 'Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra' (DARTEL). For registration purposes, six iterations and an existing DARTEL template in MNI space, derived from 555 healthy controls of the IXI-database (http://www.brain-development.org), were employed. During this registration procedure, local GM and WM volumes are conserved by modulating the image intensity of each voxel by the Jacobian determinants of the computed deformation fields. Registered image and preprocessing parameters exported were quantitatively assessed and data with weighted overall quality measure (IQR) lower than C+ were excluded from further analysis. The lower IQR was B- in the sample included in the analysis. The remaining normalized and modulated GM images were smoothed with an 8 mm full-width-at-half-maximum isotropic Gaussian kernel via a standard module of SPM. Pre-processed images were fed into SPM12 statistical models. Whole-brain correlation analysis between GM density and subscales of PCS (PCS-R, PCS-M and PCS-H) were performed using the "multiple regression" design function of SPM12. To this purpose, PCS scores were used as covariates of interest, whilst age, total intracranial volume (TIV), and total HADS were used as confounding variables to account for any potentially contributing effect on the pattern of focal GM changes. The statistical threshold was set at $p<0.05$, applying false discovery rate (FDR) correction for multiple comparisons. A more liberal criterion was also applied ($p<0.001$ uncorrected, $k=50$ voxels per cluster). Anatomical regions of interest covering the entire volumes of clusters were defined using the WFU PickAtlas tool of SPM (Maldjian, Laurienti et al. 2003, Maldjian, Laurienti et al. 2004) and Automated Anatomical Labeling (AAL) (Tzourio-Mazoyer, Landeau et al. 2002).

Functional data analysis

The CONN-fMRI Functional Connectivity toolbox v15 (http://www.nitrc.org/projects/conn) was used to extract individual subject connectivity maps.

All functional and anatomical 3D-HR-T1 weighted images were preprocessed following the standard procedure implemented in CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon 2012). Prior to first-level analysis, the standard denoising procedure including additional steps of linear detrending and despiking before regression and band-pass filtering (0.01 – 0.1 Hz) (Biswal, Yetkin et al. 1995) after regression were applied to remove unwanted motion, physiological, and other artifacts from the blood oxygen-level dependent (BOLD) signal before computing connectivity measures. The six motion correction parameters, and their first temporal derivatives, global WM, CSF and scrubbing confounds were included as regressors. All available pre-defined ROIs as implemented in CONN toolbox, including cerebellar regions (Suppl Table 1), were used as seed and source points. In addition, we included the periaqueductal gray (PAG) (MNI coordinates: x = -1, y = -28, z = -6); ROI created with a sphere of 10mm) considering its involvement in pain processing, migraine and MOH (Mainero, Boshyan et al. 2011, Riederer, Gantenbein et al. 2013, Michels, Christidi et al. 2017). General linear model was performed to explore the association between the mean time series from each seed ROI and source ROI. To explore associations of FC strength to PCS-T and PCS subscales, we performed second-level analyses. Threshold was set at $p < 0.05$ (FDR) correction, using age and total HADS as nuisance covariates.

RESULTS

Patients' demographic and clinical characteristics and psychometric data

We included 18 patients with MOH with a mean duration of headaches 26.06±6.99 years and mean headache days per month 24.44±4.84. Table 1 presents detailed demographic and clinical characteristics and overused medication (Table 1). None of the patients were under prophylactic medication for a period of three months before the MRI examination.

(Table 1)

Psychometric data

Descriptive measures were calculated for PCS-T (Mean ± SD: 32.17 ± 11.02; Median: 35) and its subscales: PCS-R (Mean ± SD: 11.39 ± 4.41; Median: 12), PCS-M (Mean ± SD: 5.56 ± 2.89; Median: 5.5), PCS-H (Mean ± SD: 15.22 ± 5.37; Median: 17). Eleven out of 18 patients were categorized as high catastrophizers based on the total PCS cut-off score (PCS-T ≥ 30).

Associations between PCS subscales and GM density

Figure 1A depicts brain regions where we found a significant **negative** association between PCS-T score and GM density ($p<0.001$ uncorrected; extent threshold $k = 50$ voxels). Areas with significant associations between GM density and PCS subscales are presented in Figure 1B-E ($p<0.001$ uncorrected; extent threshold $k = 50$ voxels).

PCS-T: Whole-brain regression analysis revealed significant association between increased PCS-T and decreased GM density in right precentral gyrus and left inferior temporal gyrus (Table 2).

PCS-R: We found significant association between increased PCS-R score and reduced GM density in right postcentral gyrus (Table 2).

PCS-M: We found significant association between increased PCS-M score and reduced GM density in left middle temporal gyrus. We also found positive association between PCS-M score and increased GM density in right inferior frontal gyrus – pars triangularis, left medial superior frontal gyrus/ACC, right postcentral gyrus, right supramarginal gyrus, and left medial superior frontal gyrus (Table 2).

PCS-H: Concerning PCS-H, we detected only positive association between increased PCS-H score and increased GM density in left superior frontal gyrus, right fusiform/inferior temporal gyrus and left putamen (Table 2).

(Table 2)

Associations between PCS subscales and FC

In the fMRI ROI-to-ROI analysis, we mainly identified negative associations between the subscale scores and the mean connectivity, except of the PSC-T and PCS-H ($p<0.05$, FDR-corrected).

PCS-T: We found positive association between PCS-T and the FC between left middle temporal gyrus and cerebellum [8], as well as negative association between PCS-T and the FC between precuneus and right ITG, as well as between left frontal pole and right temporal fusiform cortex (Figure 2).

PCS-R: Our results showed negative **association** between the PCS-R test and the FC between left globus pallidus and posterior supramarginal gyrus ($p=0.012$) as well as between precuneus and right inferior temporal gyrus ($p=0.040$) (Figure 3).

PCS-M: Increased PCS-M score was found to be linked with reduced FC between left cerebellum [2] and a) bilateral cerebellum [3] (right: $p=0.023$; left: $p=0.047$), b) bilateral cerebellum [4,5] (right: $p=0.024$; left: $p=0.047$), c) cerebellar vermis [3] ($p=0.024$) (Figure 4).

PCS-H: We found positive **association** between PCS-H and the FC of the left middle temporal gyrus and the left cerebellum [8] ($p=0.016$) (Figure 5). **We also found that increased PCS-H was associated with reduced FC (negative association)** between a) the precuneus and right inferior temporal gyrus ($p=0.019$), b) right temporal fusiform cortex and left globus pallidus ($p=0.025$), c) right temporal fusiform cortex and left superior temporal gyrus ($p=0.034$) is increased (Figure 5).

DISCUSSION

To our knowledge, no study to date has investigated structural and functional brain features related to overall PC and its dimensions in patients with MOH. In the present study, PC dimensions were associated with a specific pattern of structural and functional brain changes, which was different from the pattern observed when PC was considered as a single score.

Is the whole identical to its parts?

The neuroanatomical substrate of PC has been examined in few neuroimaging studies with structural and/or functional techniques in healthy participants (Gracely, Geisser et al. 2004) and variable chronic pain syndromes, such as migraine (Hubbard, Khan et al. 2014) and MOH (Chanraud, Di Scala et al. 2014), patients after lumbar disk surgery (Chehadi, Suchan et al. 2017), vulvar pain (Schweinhardt, Kuchinad et al. 2008). In MOH patients, higher PC scores were associated with decreased GM density in left middle frontal gyrus, putamen, right cuneus and left calcarine area and with increased GM density in the cerebellum and right mid-occipital gyrus (Chanraud, Di Scala et al. 2014). On the other hand, a negative association has been reported in chronic migraine patients; higher pain catastrophizing was linked to decreased GM density in primary somatosensory cortex, medial prefrontal cortex and ACC (Hubbard, Khan et al. 2014). Different cortical regions with bidirectional associations were detected in patients undergoing lumbar disk surgery; increased PC was associated with decreased GM density in left posterior cingulate and fusiform cortex and with increased GM density in right middle frontal gyrus/supplementary motor area and superior temporal gyrus (Chehadi, Suchan et al. 2017). Concerning GM density, our present findings clearly support that by fractionating the total score into sub-dimensions, a different pattern emerged which highlights the involvement of a) medial frontal regions and ACC in magnification, b) basal ganglia in helplessness, and c) somatosensory cortex both in rumination and magnification. Of note, somatosensory cortex was also related to the total PCS score. Concerning FC, our findings highlight a distinct pattern of intra-cerebellar activation changes in association with

magnification and a shared involvement of basal ganglia and DMN. We identified DMN regions that are involved in the core DMN but also lateral temporal regions that represent part of the dorsal medial prefrontal cortex (DMPFC)-DMN subsystem (Andrews-Hanna, Reidler et al. 2010). Higher total PCS score was associated with depression of the connectivity between DMN regions (i.e. core DMN and DMPCF-DMN), as well as with stronger engagement between DMN and cerebellum (positive association). These findings not only support the already known role of DMN but also highlight the cerebellar role in PC. Several of these regions are involved in patients with MOH or chronic migraine, i.e. medial frontal regions, ACC, basal ganglia, somatosensory cortex (Fumal, Laureys et al. 2006, Lakhan, Avramut et al. 2013, Schwedt and Chong 2017, Messina, Rocca et al. 2018). Considering that several MOH-related structural and/or functional abnormalities are reversible after withdrawal in contrast to orbitofrontal dysfunction (Fumal, Laureys et al. 2006, Riederer, Gantenbein et al. 2013), the influence of overused medication on the association between PC, GM density and functional connectivity is intriguing and needs clarification in future studies. It appears that the structural and functional underpinnings of the total PCS score ("whole") are not identical to the ones observed when we consider different PCS dimensions ("parts").

Structural and functional brain alterations associated with PCS-R

Rumination refers to repetitive thinking that is usually self-referential (Segerstrom, Stanton et al. 2003) and has been identified in patients with depression, anxiety, obsessive-compulsive disorder (Hamilton, Farmer et al. 2015), migraine (Kokonyei, Szabo et al. 2016) and chronic pain (Edwards, Tang et al. 2011). Higher PCS-R scores were linked to decreased GM density in the postcentral gyrus and lead to decreased rs-FC between left globus pallidus and posterior supramarginal gyrus, as well as between precuneus and right inferior temporal gyrus. These results corroborate previous functional and structural findings for the role of somatosensory cortex (Gracely, Geisser et al. 2004, Chehadi, Suchan et al. 2017), supramarginal gyrus (Gracely, Geisser et al. 2004, Lloyd, Helbig et al. 2016, Milazzo, Ng et al. 2016) and DMN

(Gracely, Geisser et al. 2004, Kucyi, Moayedi et al. 2014, Hamilton, Farmer et al. 2015) in ruminative thinking. As it was previously mentioned, DMN also involves temporal brain structures including inferior temporal gyrus (Buckner, Andrews-Hanna et al. 2008, Zeng, Shen et al. 2012, Guo, Liu et al. 2013, Jacobs, Watkins et al. 2016). Ruminative responding has been linked to the dominance of DMN over other brain networks (Hamilton, Furman et al. 2011, Whitfield-Gabrieli and Ford 2012). In patients with remitted major depression, reduced DMN suppression has been associated with increased rumination (Bartova, Meyer et al. 2015). The involvement of basal ganglia is well known in rumination, i.e. depressed individuals with C957T polymorphism of DRD2 gene, which affects D2 dopamine receptors that are expressed in the indirect pathway of the basal ganglia, show higher levels of maladaptive rumination (Whitmer and Gotlib 2012). Also, basal ganglia play a unique role in inhibiting competing action plans and filtering relevant information during task switching (Yehene, Meiran et al. 2008), which are highly associated with rumination (Papageorgiou and Wells 2001). Basal ganglia involvement in pain processing (Chudler and Dong 1995, Barker 2009) and mood regulation (Cummings 1993) is also well-known.

Structural and functional brain alterations associated with PCS-M

Magnification has been considered as a reactionary or proximal cognitive response to pain experience, since people tend to magnify the threat value of the pain stimulus (Quartana, Campbell et al. 2009). We found both positive and negative associations between PCS-M and GM density in left middle temporal gyrus (negative association), as well as lateral and medial frontal regions, right postcentral gyrus and right supramarginal gyrus (positive association). Bidirectional associations have been reported in previous studies (Schweinhardt, Kuchinad et al. 2008, Chehadi, Suchan et al. 2017) but the exact nature of the bidirectionality remains under investigation. We highlight the role of core DMN regions (i.e. medial frontal regions) and regions of the DMPFC-DMN subsystem (i.e. supramarginal gyrus, inferior frontal and lateral temporal gyrus) (Andrews-Hanna, Reidler et al. 2010). In addition, the somatosensory

cortex has been implicated in PC in fibromyalgia (Gracely, Geisser et al. 2004) and chronic migraine patients (Hubbard, Khan et al. 2014). Our study further highlights reduced FC in cerebellum as magnification **increases**, which might suggest a specific involvement of an intra-cerebellar network in magnification. Of note, cerebellar activity has been linked to PC in fibromyalgia (Gracely, Geisser et al. 2004, Lazaridou, Kim et al. 2017) and MOH (Chanraud, Di Scala et al. 2014), which might underlie the cerebellar role in the anticipation of pain (Leung 2012) and several other processes usually associated with the multidimensional experience of pain (Moulton, Schmahmann et al. 2010, Lloyd, Helbig et al. 2016). Increased cerebellar metabolism has been found in MOH before withdrawal (Fumal, Laureys et al. 2006).

Structural and functional brain alterations associated with PCS-H

Helplessness reflects the perceived inability to deal with painful situations (Bishop and Warr 2003). Increased PCS-H score was associated with increased GM density in left superior frontal gyrus, right fusiform and left putamen. Bidirectional correlations were observed in FC analysis; increased PCS-H score was associated with increased FC between middle temporal gyrus and left cerebellum, as well as decreased FC between precuneus and right inferior temporal gyrus, between right temporal fusiform cortex and left pallidum and between right temporal fusiform cortex and left superior temporal gyrus. Positive associations are in line with previous studies in chronic pain (Salomons, Moayedi et al. 2012, Chehadi, Suchan et al. 2017). Subcortical regions such as the dorsal raphe nucleus (Maier and Watkins 2005) and locus coeruleus (Weiss, Stout et al. 1994) as well as cortical regions (Amat, Baratta et al. 2005) have been associated with helplessness. Superior frontal gyrus has been found to be positively linked with hopelessness in a PET study in normal participants (Gottschalk, Fronczek et al. 1993) and shows a pattern of increased and/or decreased activation in depression in resting-state fMRI (Fitzgerald, Laird et al. 2008). On the other hand, patients with major depressive disorder show significantly decreased deactivation in the DMN which

correlates with the depression severity and feelings of hopelessness (Grimm, Boesiger et al. 2009). Basal ganglia are involved in the brain neuroanatomic circuit related to mood regulation (Cummings 1993) as well as motor and non-motor functions of pain (Chudler and Dong 1995, Barker 2009). Increased vulvar and non-vulvar PCS has been associated with increased GM density in left basal ganglia and bilateral parahippocampus (Schweinhardt, Kuchinad et al. 2008). In the seminal paper for the neuroanatomical substrate of catastrophizing by Gracely and colleagues (Gracely, Geisser et al. 2004), PC was associated with enhanced activation of the ipsilateral parietal cortex and contralateral lentiform nuclei (i.e. putamen, globus pallidus) while high catastrophizers displayed a unique activation in the contralateral ACC and bilateral lentiform nuclei. In our study, higher PCS-H score was associated with increased GM density in left putamen and reduced FC between right temporal fusiform cortex and left globus pallidus. Putamen has been implicated in the somatotopic modulation of pain (Bingel, Glascher et al. 2004) and variations in subjective ratings of pain (Scott, Heitzeg et al. 2006) and chronic pain increase putamen volume (Schmidt-Wilcke, Luerding et al. 2007). Furthermore, globus pallidus seems to be involved in the encoding of pain (Yelnik 2008) and morphine analgesia (Anagnostakis, Zis et al. 1992). On the other hand, increased GM density in basal ganglia is consistently reported in MOH (Riederer, Marti et al. 2012, Neeb, Bastian et al. 2017). Repeated migraine attacks are associated with increased iron accumulation in several deep nuclei (including basal ganglia) (Kruit, Launer et al. 2009) whilst the caudate nucleus seems larger in high versus low frequency migraineurs (Maleki, Becerra et al. 2011). The association between basal ganglia and helplessness both in VBM and rs-fMRI analysis could further explain the addictive behavior in MOH (Dodes 1990, Belin, Jonkman et al. 2009).

Limitations and future directions

Limitations of the study include the relatively small sample size of patients with MOH and the absence of healthy controls with relevant psychometric measures. Another limitation of our study is the absence of neuropsychological data, especially related to attention and executive functions, which might have mediation effects on the association between PC, GM density and functional connectivity, considering that pain variables of intensity, duration and catastrophizing are associated with attention, working memory and executive functions in patients with chronic pain (Baker, Georgiou-Karistianis et al. 2018, Weiss, Harbeck-Weber et al. 2018, Elkana, Conti et al. 2019). Future attempts to study the neuroanatomical substrate of PC dimensions in different chronic pain conditions might further enable researchers to figure out whether structural and functional underpinnings of PC are indeed similar across different chronic pain syndromes irrespectively of the underlying pathophysiological mechanism of pain. **Future studies may also include MOH patients with other primary headache (i.e. tension-type headache) who may have even higher scores on PCS**. In addition, an important clinical implication of our findings is highly linked to any predictive role of PC-related brain network to better characterize MOH patients with increased risk for poor prognosis after withdrawal. PC-related structural and functional features have been suggested as possible targets for psychological interventions in other chronic pain groups (Lazaridou, Kim et al. 2017). **Furthermore, considering the neuroanatomical substrate of PC and cognitive-related changes in MOH or chronic migraine and chronic pain syndromes, PC may have implications for cognitive functioning. This could encourage either adaptive pain coping mechanisms to improve cognitive performances or cognitive rehabilitation strategies to reduce PC**. Finally, cerebellum appears to be a structure with a crucial role in pain (Schwedt, Chong et al. 2014) and PCS, thus investigation of corticocerebellar connections (Karavasilis, Christidi et al. 2018) may constitute a future challenge.

Conclusion

Our study highlights that PC dimensions are associated with a specific structural and functional brain pattern, which is different from the pattern observed when PC is considered as a single score. The structural and functional pattern of PCS dimensions differs from the pattern that is emerged when the total PCS score is considered in a group of patients with MOH. In particular, the investigation of rumination, magnification and helplessness as specific PC dimensions not only confirms the role of DMN either in its core nodes or in regions of DMPFC DMN subsystem but also unveils the involvement of basal ganglia in rumination and helplessness and a possible role of cerebellum in magnification.

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Figure Legends

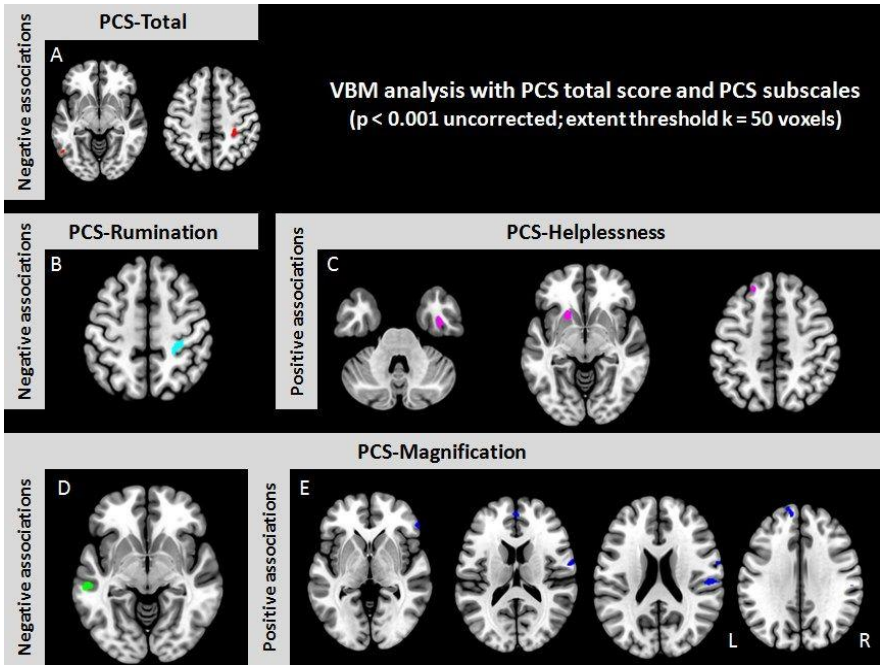

Figure 1: VBM regression analysis showing significant association between (A) increased PCS-Total score and decreased GM density, (B) increased PCS-Rumination score and decreased GM density, (C) increased PCS-Helplessness score and increased GM density, and increased PCS-Magnification score and (D) decreased and (E) increased GM density in patients with MOH. Significant clusters are thresholded at p< 0.001 uncorrected, expected voxels per cluster k = 50 voxels. VBM = voxel-based morphometry; PCS = Pain Catastrophizing Scale; GM = gray matter; MOH = medication-overuse headache.

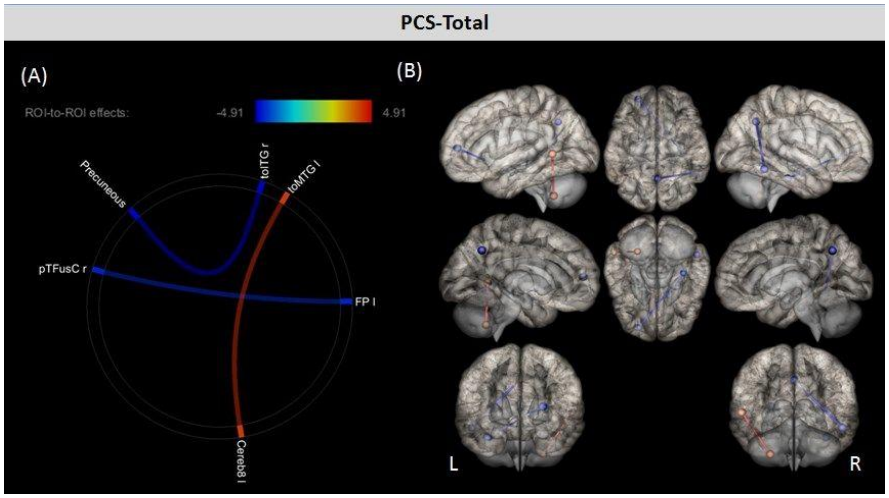

Figure 2: Region-to-region connectivity analysis regarding PCS-Total score in patients with MOH. Significantly **positive** associations (red lines) between increased PCS-Total score and **increased** connectivity and **negative** associations (blue lines) between increased PCS-Total score and **decreased** connectivity are shown using (A) connectome ring with regions labeled around the perimeter and (B) 3-dimensional brain volumes using a t statistic after false discovery rate correction (corrected $p < 0.05$). PCS = Pain Catastrophizing Scale; MOH = medication-overuse headache; aITG r = inferior temporal gyrus, anterior division right; Cereb8 l = Cerebellum 8 left; pTFusC r = temporal fusiform cortex, posterior division right; FP l = frontal pole left; toITG r = inferior temporal gyrus, temporooccipital part right.

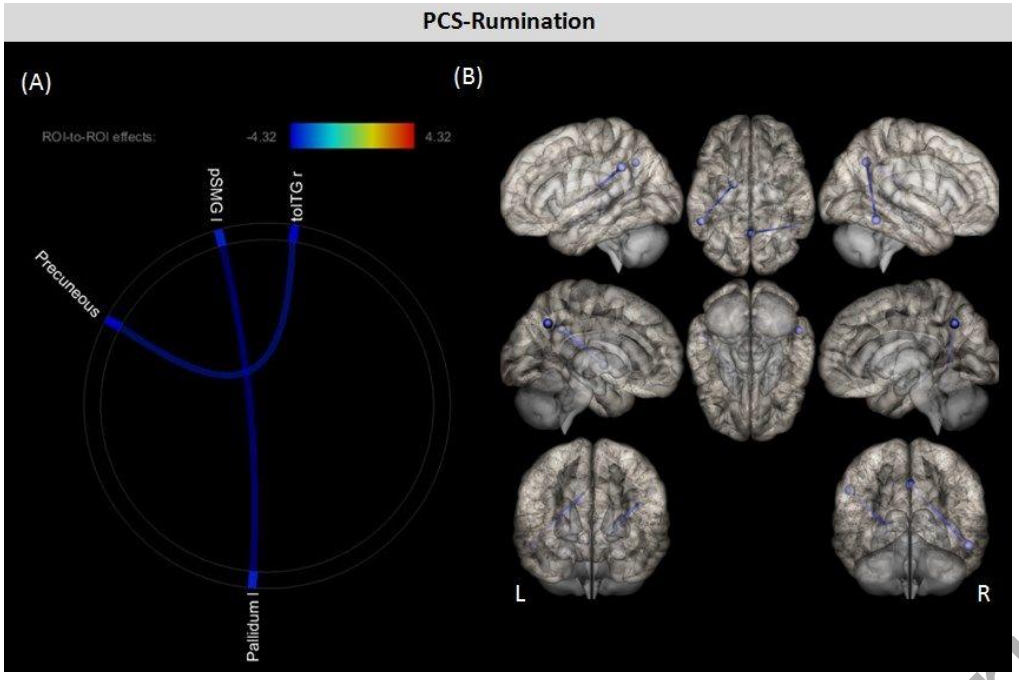

Figure 3: Region-to-region connectivity analysis regarding PCS-Rumination score in patients with MOH. Significantly negative associations (blue lines) between increased PCS-Rumination score and decreased connectivity are shown using (A) connectome ring with regions labeled around the perimeter and (B) 3-dimensional brain volumes using a t statistic after false discovery rate correction (corrected $p < 0.05$). PCS = Pain Catastrophizing Scale; MOH = medication-overuse headache; pSMG l = supramarginal gyrus, posterior division left; toITG r = inferior temporal gyrus, temporooccipital part right.

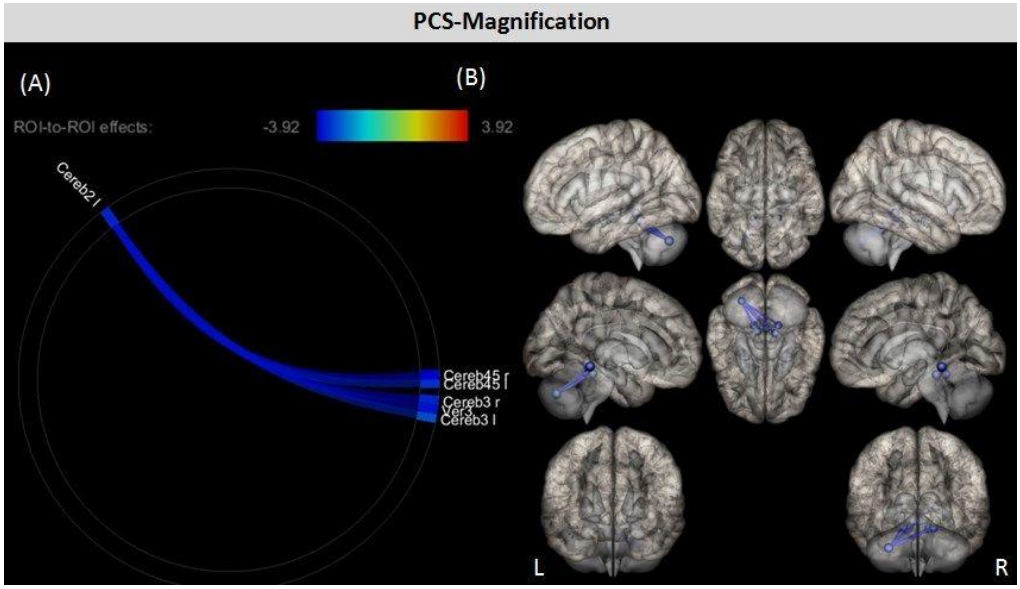

Figure 4: Region-to-region connectivity analysis regarding PCS-Magnification score in patients with MOH. Significantly negative associations (blue lines) between increased PCS-Magnification score and decreased connectivity are shown using (A) connectome ring with regions labeled around the perimeter and (B) 3-dimensional brain volumes using a t statistic after false discovery rate correction (corrected $p < 0.05$). PCS = Pain Catastrophizing Scale; MOH = medication-overuse headache; Cereb1 r = cerebellum crus 1 right; Cereb3 l = cerebellum 3 left; Cereb3 r = cerebellum 3 left; Cereb45 l = cerebellum 4 5 left; Cereb45 r = cerebellum 4 5 right; Ver3 = vermis 3.

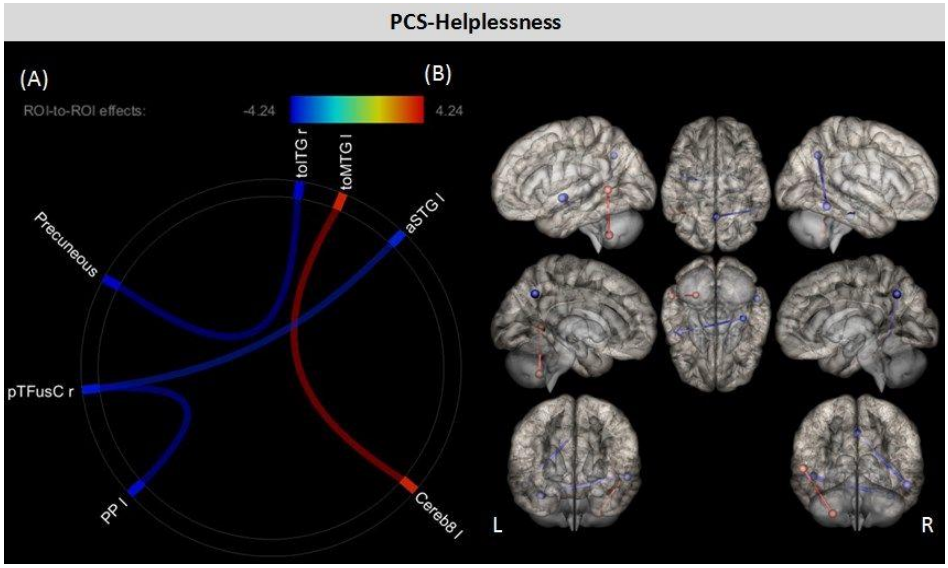

Figure 5: Region-to-region connectivity analysis regarding PCS-Helplessness score in patients with MOH. Significantly positive associations (red lines) between increased PCS-Helplessness score and increased connectivity and negative associations (blue lines) between increased PCS-Helplessness score and decreased connectivity are shown using (A) connectome ring with regions labeled around the perimeter and (B) 3-dimensional brain volumes using a t statistic after false discovery rate correction (corrected $p < 0.05$). PCS = Pain Catastrophizing Scale; MOH = medication-overuse headache; Cereb8 l = cerebellum 8 left; toMTG l = middle temporal gyrus, temporooccipital part left; PP l = planum polare left; pTFusC r = temporal fusiform cortex, posterior division right; toITG r = inferior temporal gyrus, temporooccipital part right; aSTG l = superior temporal gyrus, anterior division left.

Tables

Table 1. Descriptive and clinical data for patients with MOH

	Mean ± SD; Min-Max / Frequency
Age (y)	45.11 ± 8.72; 31-65
Gender (M / F)	2/16
Headache duration (y)	26.06 ± 6.99; 15-37
Headache days per month	24.44 ± 4.84; 18-30
HADS-T	16.22 ± 6.25; 3-25
Simple analgesics	9
NSAIDs	3
Triptans	4
Opiods	5
Combination analgesics	5

Notes. MOH = medication-overuse headache; y = years; M/F = male/female; HADS-T = hospital anxiety and depression scale-total score; NSAIDs = Non-steroidal anti-inflammatory drugs; SD = standard deviation; min = minimum; max = maximum.

Table 2. GM regions that were significantly associated with total PCS and its subscales (PCS-R, PCS-M, PCS-H) in patients with MOH

Contrast	Label			MNI x y z	Cluster size	T
	Side	Region	BA			
		PCS-Total				
Negative	R	Precentral Gyrus	*4 / 3*	33 -33 54	188	4.88
	L	Inferior Temporal	37	-54 -62 -8	85	4.86
		PCS-Rumination				
Negative	R	*Postcentral Gyrus*	*4 / 3*	32 -28 51	160	4.93
		PCS-Magnification				
Positive	R	*Inferior Frontal Gyrus – Pars Tri*	*46 / 45*	54 40 4	105	5.31
	L	*Medial Superior Frontal Gyrus / ACC*	*10*	0 51 14	64	5.07
	R	*Postcentral Gyrus*	*4 / 6*	63 -3 16	85	5.46
	R	*Supramarginal Gyrus*	*40*	54 -22 22	148	5.13
	L	*Medial Superior Frontal Gyrus*	*9 / 8*	-14 60 30	95	5.21
	L	*Medial Superior Frontal Gyrus*	*8*	-14 51 44	80	4.68
Negative	L	*Middle Temporal Gyrus*	22 / 21	-57 -27 -6	139	5.22
		PCS-Helplessness				
Positive	L	*Superior Frontal Gyrus*	8	-22 34 51	80	5.35
	R	*Fusiform / Inferior Temporal Gyrus*	20 / 21	39 -4 -33	102	5.07
	L	Putamen	-	-21 16 -6	159	4.66

Note. GM = gray matter; PCS = Pain Catastrophizing Scale; R = rumination; M = magnification; H = helplessness; MOH = medication-overuse headache; BA = Brodmann area; MNI = Montreal Neurological Institute; R / L = right / left; Pars Tri = pars triangularis; ACC = anterior cingulate cortex.